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GB 1380228
Chem. Ber. *107* 3476—85 (1974) Z. Natioforsch B *27* 1140—5 (1972) Izv. Sib. Otd. Akad. Nauk SSSR Ser. Khim Nauk 44—8 (1973) (cf CA *79* 120052 w) Zh. Neorg. KHIM. *20* 3352—6 (1975) (cf CA *84* 83508e)
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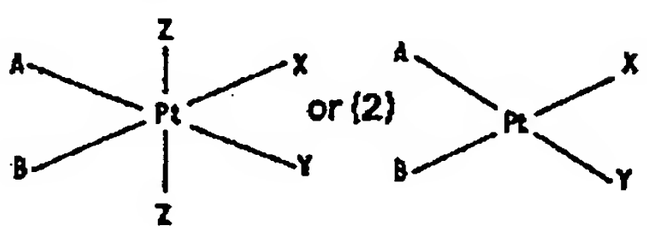
(71) Applicant
Johnson, Matthey & Co., Limited, 43 Hatton Garden, London, EC1N 8EE
(72) Inventors
Paul Cedric Hydes,
David Malcolm Watkins
(74) Agent
Withers & Rogers

The chemical formulae appearing in the printed specification were submitted in formal form after the date of filing.

(54) Pt (II) and (IV) Amino-Acid Complexes

(57) Platinum co-ordination compounds having the structure

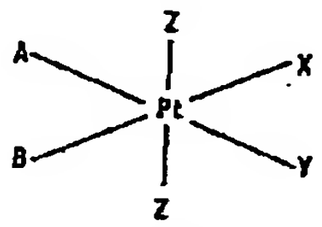


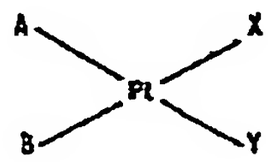
[in which X and Y are the same or different ligands selected from halogen, pseudohalogen, sulphate, phosphate, nitrate, carboxylate, substituted carboxylate and water and A and B are the same or different amino acids co-ordinated to the Pt through their N atoms, and Z is halogen, pseudohalogen or hydroxy] are useful in the treatment of malignant tumours or neoplasms.

SPECIFICATION
Compositions Containing Platinum

This invention relates to platinum co-ordination compounds, to pharmaceutical compositions containing them and to their use in the treatment of malignant tumours or malignant neoplasms.

According to a first aspect of the present invention, a composition of matter comprises a *cis* co-ordination compound of platinum having the structure

(1) 

or (2) 

in which X and Y are the same or different ligands selected from halogen, pseudohalogen, sulphate, phosphate, nitrate, carboxylate, substituted carboxylate and water and A and B are the same or different amino acids co-ordinated to the Pt through their N atoms, and Z groups may or may not be present and, if present, are halogen, pseudohalogen or hydroxy groups. By phosphate, we mean both $H_2PO_4^-$ and HPO_2^{2-}.

Where X and/or Y is represented by carboxylate or substituted carboxylate, the general formula of which is $C_nR_{2n+1}CO_2H$, we prefer that n is an integer from 1 to 9 inclusive and that the R groups are the same or different and are selected from hydrogen, substituted or unsubstituted straight- or branched-chain alkyl, aryl, alkaryl, aralkyl, alkenyl, cycloalkyl and cycloalkenyl, halogen, pseudohalogen (as hereinafter defined), hydroxy, formyl, nitro, amido, amino and sulphonic acid salts. We intend the above definition also to include oxygen and sulphur, such that one doubly bonded oxygen or sulphur atom is represented by two R groups.

Where X and Y are both carboxylate, they can together comprise a dicarboxylate bidentate ligand, for example oxalate and ligands having the general formula

$$-OOC-(CR^1_yR^2_z)_{n^1}-COO^-$$

where n^1 is an integer from 2 to 6, R^1 and R^2 are the same or different and are selected from H, lower alkyl, aryl, alkaryl, aralkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, OH, halogen, pseudohalogen (as hereinafter defined) or are combined with the carbon atoms to form a cycloalkyl or cycloalkenyl or aryl group, and substituted derivatives thereof, and y and z are either 0 or 1 as long as (y+z) is equal to 1 or 2.

Suitable dicarboxylate ligands are the succinato, glutarato (pentanedioato), adipato (hexanedioato), pimelato (heptanedioato), malato (cis-butenedioato), and phthalato (o-benzenedicarboxylate) ligands and these may be either substituted or unsubstituted.

The amino acid has the general formula:

$$R^3R^4N—(CR^5R^6)_x—CO_2H$$

in which x is 1, 2 or 3 and R groups are the same or different and are selected from hydrogen, substituted or unsubstituted straight- or branched-chain alkyl, aryl, alkaryl, aralkyl, alkenyl, cycloalkyl and cycloalkenyl groups, halogen, pseudohalogen (as hereinafter defined) hydroxy, formyl, amido, amino, alkoxy, aryloxy, sulphonic acid or salt and carboxylic acid, ester or salt or two R groups may together represent oxygen or sulphur.

Where one or more of the R^3—R^6 groups is carboxylate or derivative thereof such as ester, the general formula of which is $C_mR^7_{2m+1}CO_2^-$, it may be a substituted carboxylate such that m is an integer from 1 to 9 inclusive and the R^7 groups are the same or different and are selected from hydrogen, substituted or unsubstituted straight- or branched-chain alkyl, aryl, alkaryl, aralkyl, alkenyl, cycloalkyl and cycloalkenyl, halogen, pseudohalogen (as hereinafter defined) hydroxy, alkoxy, aryloxy, formyl, nitro, amido, amino and sulphonic acid salts. We intend the above definition also to include oxygen and sulphur, such that one doubly bonded oxygen or sulphur atom is represented by two R^7 groups.

Examples of particular amino acids which may be used to form a complex with platinum according to the invention are glycine ($NH_2CH_2CO_2H$), alanine ($CH_3CH(NH_2)CO_2H$), valine ($(CH_3)_2CHCH(NH_2)CO_2H$), phenylalanine ($PhCH_2CH(NH_2)CO_2H$) aspartic acid ($HO_2CCH_2CH(NH_2)CO_2H$), asparagine ($NH_2COCH_2CH(NH_2)CO_2H$) and cysteine ($HSCH_2CH(NH_2)CO_2H$).

The term "pseudohalogen" in this specification has the meaning given on p. 560 of "Advanced Inorganic Chemistry" by Cotton and Wilkinson, Interscience Publishers, 1966 as being "a molecule consisting of more than two electronegative atoms which, in the free state, resembles the halogen; these pseudohalogens give rise to anions which resemble the halide ions in behaviour". Examples of suitable pseudohalogens are cyanide, cyanate, thiocyanate and azide.

We have found that compounds of the present invention are active against cancer, or malignant

tumour or malignant neoplasms. Normally the compound is used in association with a pharmaceutically acceptable carrier therefor. Accordingly, in a second aspect, the present invention provides a pharmaceutical composition which comprises a compound according to the first aspect of the invention and a pharmaceutically-acceptable carrier for said compound; these compositions can be formulated so as to be suitable for example, for parenteral or oral administration to animals affected with a malignant tumour or neoplasm.

Preparative details of complexes of platinum according to the invention will now be described by way of example.

1. cis-[dichloro(glycine)platinum (II)]

Preparation of cis-$PtCl_2(NH_2CH_2COOH)_2$

$K_2[PtCl_4]$ (50 g) is 200 ml. hot water was charcoaled and filtered hot through a pre-heated sinter into glycine (53.52 g) and KOH (40 g) (6 mole equivalents) in 100 ml warm water. The solution was transferred to a beaker and heated on a hot plate for 20 minutes to decolourisation of the solution. The solution was then cooled to room temperature and stirred vigorously whilst concentrated HCl (30 ml) was slowly added. The precipitated white complex $[Pt(NH_2CH_2COO)_2 \cdot (NH_2CH_2COOH)_2]$ was filtered off on a pore 3 sinter, washed copiously with water and dried in vacuo at 50°C.

The while sold was suspended in 250 ml water at 80°C for 3 hours, the cooled solution filtered through a pore 3 sinter and the product washed with water and dried in vacuo at 60°C.

Yield=29.90 g (73%).

cis-$[Pt(NH_2CH_2COO)_2]$ (12 g) was treated with concentrated HCL (60 ml) in the cold and the mixture stirred and heated to 50°C for 10 minutes. The mixture containing the yellow dichlorocomplex was cooled in ice and filtered through a pore 3 sinter. The product was washed with cold concentrated HCl, ethanol and ether and dried in vacuo at 60°C.

Yield=11.7 g (81%).

Assay	*Pt*	*C*	*H*	*N*	*O*	*Cl*
Calculated % for cis-$[PtCl_2(NH_2CH_2COOH)_2]$	46.89	11.54	2.43	6.73	15.38	17.04
Found %	—	11.36	1.89	6.60	—	—

2. cis-dichlorobis(alanine)platinum II

Preparation of *cis*-$[PtCl_2(anH)_2]$ (2)

where an= $NH_2—CH(CH_3)—COO^-$

A solution of $K_2[PtCl_4]$ (50 g) in hot water (250 ml) was added to alanine (42.34 g) and potassium hydroxide (26.68 g) in hot water (75 ml) and the resulting solution heated on a hot plate until it had become pale yellow (approximately 1 hour). Concentrated HCl was then added dropwise to bring the solution pH to approximately 3 and the solution heated on a hot plate for 4 hours to a volume of 325 ml. The white precipitate from the cooled solution was filtered off on a pore 3 sinter, washed with water, ethanol and ether and dried in vacuo at 60°C.

Yield=8.8 g (20%).

Further crops of cis-$[Pt(an)_2]$ were obtained by evaporating the mother liquor to 225 ml, followed by cooling to room temperature.

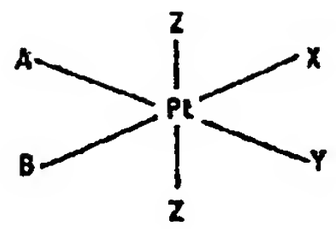
cis-$Pt(an)_2$ (4.0 g) was warmed on a hot plate to approximately 60°C for 1 minute with concentrated HCl (10 ml). The mixture was cooled to room temperature and transferred to a pore 3 sinter with a minimum volume of cold concentrated HCl. The yellow product was sucked dry, then washed copiously with ether and finally dried in vacuo at 60°C.

Yield=3.04 g (64%).

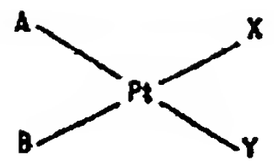
Assay	*Pt*	*C*	*H*	*N*	*O*	*Cl*
Calculated % for cis-$PtCl_2(NH_2CH(CH_3)COOH)_2$	43.93	16.21	3.17	6.30	14.41	15.96
Found %	—	16.09	2.99	6.48	—	—

Claims

1. A composition of matter comprising a *cis* co-ordination compound of platinum having the structure



or (2)



in which X and Y are the same or different ligands selected from halogen, pseudohalogen, sulphate, phosphate, nitrate, carboxylate, substituted carboxylate and water and A and B are the same or different amino acids co-ordinated to the Pt through their N atoms, and X groups may or may not be present and, if present, are halogen, pseudohalogen or hydroxy groups.

2. A composition according to Claim 1 where X and/or Y is represented by carboxylate or substituted carboxylate having the general formula

$$C_nR_{2n+1}CO_2H$$

where n is an integer from 1 to 9 inclusive and that the R groups are the same or different and are selected from hydrogen, substituted or unsubstituted straight- or branched-chain alkyl, aryl, alkaryl, aralkyl, alkenyl, cycloalkyl and cycloalkenyl, halogen, pseudohalogen (as hereinafter defined), hydroxy, formyl, nitro, amido, amino and sulphonic acid salts.

3. A composition according to Claim 2, wherein two R groups represent one doubly bonded oxygen or sulphur atom.

4. A composition according to Claim 1 or Claim 2, wherein X and Y are both carboxylate and together comprise a dicarboxylate bidendate ligand.

5. A composition according to Claim 1 or Claim 2, wherein X and Y are oxalate ligands having the general formula

$$^{-}OOC\text{-}(CR^1_yR^2_z)_{n^1}\text{-}COO^{-}$$

where n^1 is an integer from 2 to 6, R^1 and R^2 are the same or different and are selected from H, lower alkyl, aryl, alkaryl, aralkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, OH, halogen, pseudohalogen (as hereinafter defined) or are combined with the carbon atoms to form a cycloalkyl or cycloalkenyl or aryl group and substituted derivatives thereof, and y and z are either 0 or 1 as long as (y+z) is equal to 1 or 2.

6. A composition according to Claim 4, wherein the dicarboxylate ligands are substituted or unsubstituted and are selected from the group consisting of succinato, glutarato (pentanedioato) adipato (hexanedioato), pimelato (heptanedioato), malato (cis-butenedioato) and phthalato (o-benzenedicarboxylate) ligands.

7. A composition according to Claim 1, wherein the amino acid used to form a complex with platinum has the general formula

$$R^3R^4N\text{—}(CR^5R^x)x\text{—}CO_2H$$

in which x is 1, 2 or 3 and R groups are the same or different and are selected from hydrogen, substituted or unsubstituted straight- or branched-chain alkyl, aryl, alkaryl, aralkyl, alkenyl, cycloalkyl and cycloalkenyl groups, halogen pseudohalogen (as hereinafter defined) hydroxy, formyl, amido, amino, alkoxy, aryloxy, sulphonic acid or salt and carboxylic acid, ester or salt or two R groups may together represent oxygen or sulphur.

8. A composition according to Claim 7, wherein at least one of the R^3—R^6 groups is carboxylate or a derivative thereof having the general formula

$$C_mR^7_{2m+1}CO_2^{-},$$

in which m is an integer from 1 to 9 inclusive and the R^7 groups are the same or different and are selected from hydrogen, substituted or unsubstituted straight- or branched-chain alkyl, aryl, alkaryl, aralkyl, alkenyl, cycloalkyl and cycloalkenyl, halogen, pseudohalogen (as hereinafter defined) hydroxy, alkoxy, aryloxy, formyl, nitro, amido, amino and sulphonic acid salts.

9. A composition according to Claim 7, wherein the amino acid is selected from the group consisting of glycine ($NH_2CH_2CO_2H$) alanine ($CH_3CH(NH_2)CO_2H$), valine ($(CH_3)_2CHCH(NH_2)CO_2H$), phenylalanine ($PhCH_2CH(NH_2)CO_2H$) aspartic acid ($HO_2CCH_2CH(NH_2)CO_2H$), asparagine ($NH_2COCH_2CH(NH_2)CO_2H$) and cysteine ($HSCH_2CH(NH_2)CO_2H$.

10. A composition according to any preceding claim in combination with a pharmaceutically acceptable carrier.

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